



RECEIVED
APR 28 2003
TECH CENTER 1600/2900

AMINOTHIOL COMPOUND

BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention relates aminothiols compounds which perform as superior catalysts in the asymmetric addition reactions of organic zinc and aldehyde.

2. Description of the Related Technology

10 For preparing secondary alcohols, one of the most important methods is to react organic zinc with aldehyde in addition reactions. In order to accelerate this reaction, chiral aminoalcohols are usually added as ligands to combine with organic zinc. Such chiral aminoalcohol create an asymmetric reaction environment, so that one of the produced
15 chiral secondary alcohols is produced more than its stereoisomer, i.e., the asymmetric addition reactions. Apparently, the crux of obtaining a high chemical yield as well as enantioselectivity in the above reactions is to select proper chiral compounds which can provide excellent asymmetric environment for catalytical process.

20 Though many chiral compounds used in the addition reactions regarding organic zinc and aldehyde can achieve good enantioselectivity, however, these compounds have to be added at an amount at least 1% of the main reactants, and usually around 20%. Additionally, the enantioselectivity always decays with decreasing amount of the chiral
25 ligands used. In general, the enantioselectivity is reduced below 90%

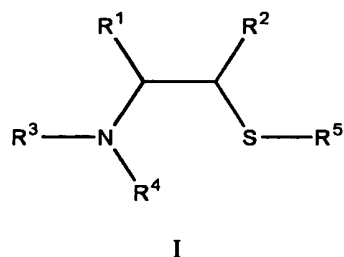
enantiomeric excess (e.e.) when the chiral ligands are descended under 5%, so that most of above reactions are not good enough for industrial usage.

Aminoalcohols with optical activity, such as N,N-dibutylnorephe-
5 edine, are frequently applied to accelerating the asymmetric addition reactions of organic zinc and aldehyde as chiral ligand catalysts. By adding aminoalcohols, enantioselectivity of the above reactions can be reached as high as 99% e. e., but an amount 10-20% of chiral aminoalcohols is need. Therefore, it's an important issue how to reduce
10 the necessary amount of the chiral ligands used in the catalysis, so that it can be an economically efficient process

SUMMARY OF THE INVENTION

The object of the present invention is to provide aminothiols
15 compounds with two chiral centers, which can increase enantioselectivity of asymmetric addition of of organic zinc and aldehyde.

In order to achieve the above object, the present invention discloses the aminothiol compounds, which has a general formula I;



20

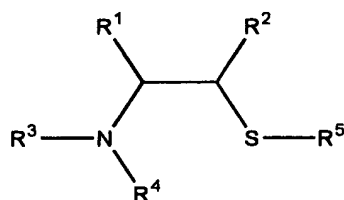
wherein R¹-R⁵ are substitutable ligands.

According to the present invention, the aminothiol compounds can

perform as superior catalysts in asymmetric addition reactions wherein organic zinc and aldehyde are involved, In such reactions, though the catalysts are added only 0.1% or even 0.02%, enantioselectivity higher than 99% e.e. can always be obtained. So that such catalyses are economically
5 useful for industries.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present invention, aminothiols compounds has a general formula I,



I

wherein R¹ is aryl or alkyl of C1-C9;

R² is aryl or alkyl of C1-C9;

R³ is alkyl of C1-C9;

R⁴ is alkyl of C1-C9;

or R³, R⁴ and N can form a three-to-eight-membered heterocycle;

and

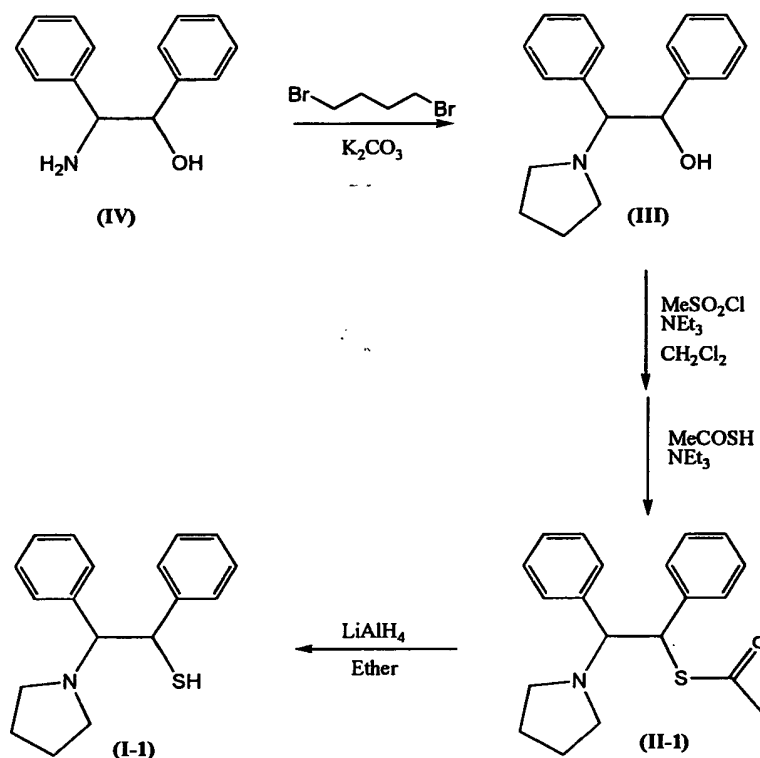
R⁵ can be H or alkyl of C1-C6.

A method for preparing the above ligands and application thereof are as follows:

1. Preparing the ligands

A typical compound of the present invention can be obtained

according to the following scheme,



- 5 wherein the compound of formula I-1 is obtained by reacting the compound of formula II-1 with LiAlH_4 (lithium aluminum hydride). This method includes steps of:

S11: LiAlH_4 and THF (Tetrahydrofuran) are added into a dried three-neck flask under a nitrogen system, the temperature is then regulated to 0°C , and the compound of formula II-1 dissolved in THF is added into the flask through an auto-injector in 30 minutes.

S12: After the above reactants have completely reacted by stirring for one hour, 15 % aqueous NaOH is added to terminate the reaction.

S13: The solution of S12 is filtered through a filter paper, wherein

the remained solid is repeatedly washed with a solvent and the filtrate is concentrated by reducing pressure through a vacuum pump to obtain coarse product.

5 S14: The crude product is then purified through flash column chromatography (Silica gel; eluent is Hex : Et₃N= 100 : 1) to obtain white solid.

Further, the compound of formula II-1 is produced by reacting (1*R*, 2*S*)-(-)-1,2-diphenyl-2-aminoethanol, i.e., the compound of formula IV, with 1,4-dibromobutane and potassium carbonate to produce the
10 compound of formula III with the cyclic structure as morpholine

S21: The compound of formula III is dissolved in dichloromethane under nitrogen, then triethylamine is injected therein, and the temperature is reduced to 0°C.

S22: MeSO₂Cl dissolved in dichloromethane is dropwisely added
15 into the solution obtained in S21 through a funnel.

S23: After the above solution has completely reacted by stirring for two hours , the aliquote is concentrated by reducing pressure through a vacuum pump, benzene is added therein under nitrogen, and the mixture is heated and refluxed.

20 S24: Thiolacetic acid and triethylamine are dissolved in benzene and then injected into the mixture of S23.

S25: After the above mixture has completely reacted by stirring for eight hours, H₂O is added therein to terminate the reaction, and the mixture is extracted with dichloromethane for three times.

25 S26: Anhydrous Na₂SO₄ is added into the organic layer obtained in

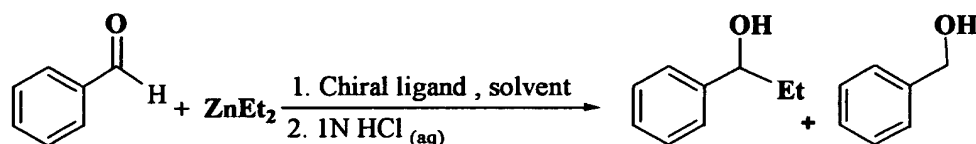
S25 to absorb H₂O, which is then filtered and concentrated by reducing pressure through vacuum pump to obtain crude product.

S27: The crude product is purified by column chromatography (Silica gel, eluent is n-Hexane: EtOAc: Et₃N = 100: 1: 1) to obtain a
5 yellow liquid, i.e., the compound of formula II-1.

2. Application of the present invention

The addition reaction of organic zinc and aldehyde can be shown as the following scheme.

10



The above scheme includes steps of:

S31: The ligand of formula I-1 (0.03 g, 0.1 mmol) and a dried
15 magnetic stirrer are added into a dried flask.

S32: The flask is sealed and vacuumed to remove moisture and then filled with nitrogen, and then diethylzinc (1.10 mL, 1.2 mmol) is added therein at room temperature and stirred for two hours.

S33: The temperature is adjusted to -20°C , and benzaldehyde (0.11
20 mL, 1.0 mmol) is added therein and stirred for 12 hours.

S34: 1N aqueous HCl (1 mL) is added into the above solution to terminate the reaction.

S35: The solution of S34 is extracted with acetyl acetate (20 mL),

wherein the organic layer is collected and dehydrated with anhydrous MgSO_4 , and then the mixture is filtered, and the filtrate is concentrated by reducing pressure through an air pump to obtain crude product.

S36: The crude product is purified by column chromatography
5 (Silica gel, eluent is n-Hexane: EtOAc = 10: 1).

In order to confirm that high enantioselectivity can be obtained from the present invention, different aminothiols compounds (4d4c, 5d5c) are provided to perform the reactions. The results are listed in Table 1, in which only few values of enantioselectivity are lower than 99% e.e. when
10 the amount of these ligands is 0.02%. Additionally, when the amount of these ligands is 0.1%, all values of enantioselectivity are higher than 99% e.e.

Obviously, the aminothiols compounds in accordance with the present invention are superior than the catalysts existing in the literature for the
15 asymmetric addition of organic zinc to aldehyde. In such reactions, though the catalysts are added only 0.1% or even 0.02%, enantioselectivity higher than 99% e.e. are always obtained. Therefore, aminothiols compounds in the present invention are indeed very economic for applying the above asymmetric reactions to industries.

20 Similarly, the aminothiols compounds in the present invention can be provided as chiral ligands to react with other organic metals, for example, Cu, Ti, etc., to form organometal complexes. These complexes can also react with carbonyl such as aldehyde and ketone, to produce alcohol in the asymmetric addition reactions.

25 It should be noticed that the above embodiments are only used for

explaining the present invention, but not limiting the scope.

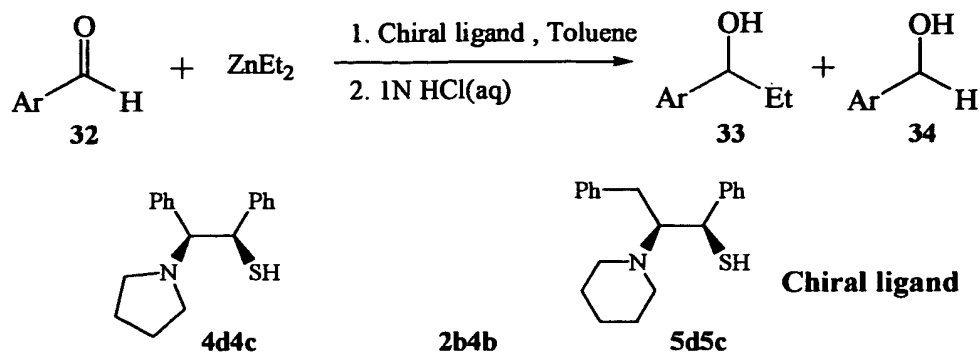


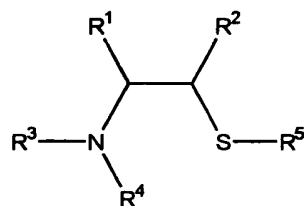
Table 1: The Ratios of Substrate to Chiral Ligands (S/C)

Entry ^a	Ligand	S/L	Conversion (%)	33 : 34	e.e.(%)
1	4d4c	5000	80	1 : 0	99.0 (R)
2	4d4c	2000	100	1 : 0	99.1 (R)
3	4d4c	1000	100	1 : 0	99.2 (R)
4	4d4c	333	100	1 : 0	99.3 (R)
5	4d4c	166	100	1 : 0	99.3 (R)
6	4d4c	100	100	1 : 0	99.3 (R)
7	4d4c	50	100	1 : 0	99.4 (R)
8	4d4c	20	100	1 : 0	99.4 (R)
9	4d4c	10	100	1 : 0	99.5 (R)
10	4d4c	5	100	1 : 0	99.5 (R)
21	5d5c	10000	68	1 : 0.015	98.1 (R)
22	5d5c	5000	81	1 : 0.005	98.9 (R)
23	5d5c	2000	82	1 : 0.005	99.0 (R)
24	5d5c	1000	100	1 : 0	99.1 (R)
25	5d5c	500	100	1 : 0	99.1 (R)
26	5d5c	200	100	1 : 0	99.2 (R)
27	5d5c	100	100	1 : 0	99.3 (R)
28	5d5c	50	100	1 : 0	99.3 (R)
29	5d5c	20	100	1 : 0	99.3 (R)
30	5d5c	10	100	1 : 0	99.4 (R)
31	5d5c	5	100	1 : 0	99.4 (R)
32	5d5c	2	100	1 : 0	99.4 (R)
33	5d5c	1	100	1 : 0	99.0 (R)

^a All of the above reactions used benzaldehyde as the substrate, toluene as the solvent. ^b 3.7 eq. of Et₂Zn was used. ^c The reaction were carried at -20°C for 12hrs. ^d S/C was the ratio between the substrate and chiral ligand.

WHAT IS CLAIMED IS:

1. An aminothiol compounds, having a general formula I,



I

5

wherein R¹-R⁵ are substitutable ligands.

2. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R¹ is aryl.

3. The aminothiol compounds and acylated derivatives thereof as
10 claimed in claim 1, wherein R¹ is alkyl of C1-C9.

4. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R² is aryl.

5. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R² is alkyl of C1-C9.

15 6. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R³ is alkyl of C1-C9.

7. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R⁴ is alkyl of C1-C9.

8. The aminothiol compounds and acylated derivatives thereof as
20 claimed in claim 1, wherein R⁵ is H.

9. The aminothiol compounds and acylated derivatives thereof as claimed in claim 1, wherein R⁵ is alkyl of C1-C6.

12. The aminothiols compounds and acylated derivatives thereof as claimed in claim 1, wherein R^3 , R^4 and N form a cycle.

13. The aminothiols compounds and acylated derivatives thereof as claimed in claim 12, wherein R^3 , R^4 and N form a three-to-eight-
5 membered heterocycle.

14. The aminothiols compounds and acylated derivatives thereof as claimed in claim 12, wherein R^3 , R^4 , O and N form a ring by means of morpholine.

15. The aminothiols compounds and acylated derivatives thereof as
10 claimed in claim 1, wherein R^3 , R^4 , O and N form a ring by means of morpholine.

16. The aminothiols compounds and acylated derivatives thereof as claimed in claim 1, which are chiral ligands capable of reacting with organic metal compounds to form metal complexes and then react with
15 carbonyl to produce alkylmetal in asymmetric addition reactions.

17. The aminothiols compounds and acylated derivatives thereof as claimed in claim 16, wherein said carbonyl compound is aldehyde.

18. The aminothiols compounds and acylated derivatives thereof as claimed in claim 16, wherein said carbonyl compound is ketone.

20 19. The aminothiols compounds and acylated derivatives thereof as claimed in claim 16, wherein said organic metal is Zn, Cu, or Ti.

ABSTRACT

The present invention discloses an aminothiols compound having a general formula I wherein R^1 - R^5 are substitutable ligands. Such compounds can perform as superior catalysts in asymmetric addition reactions of organic zinc and aldehyde. According to the present invention, the compounds is needed only less than 0.02% of main reactants to obtain enantioselectivity higher than 99% enantiomeric excess, whereby the asymmetric reactions can become very economic.

